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EXAMINER
BERTOGLIO, VALERIE E

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/914,190	Applicant(s) MIKI ET AL.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: .

DETAILED ACTION

Claims 1-8 are pending and under consideration in the instant office action.

Specification

The disclosure is objected to because of the following informalities:

The specification discloses the use of pAxcwt with the Adenovirus Expression Vector Kit (page 7, line 5). pAxcwt should read either "pAxcw" or "pAxCAwt" (Takara Shuzo Catalog. Adenovirus Expression Vector Kit. http://bio.takara.co.jp/BIO_EN/Catalog_d.asp?C_ID=C0982).

Claim Objections

Claim 6 objected to because of the following informalities: The word transgenic (line 1) is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a transgenic mollusk (claims 1-8) or shellfish (claim 2) comprising a foreign gene that produces a colorant or colorant precursor (claims 4 and 5) in at least one tissue and methods for producing said transgenic mollusk (claims 6-8). The purpose of the invention is to make a colored pearl in mollusks (page 2, lines 20-22). Pearl is considered either pearl formed of concentric layers of nacre (as in a jewel) or the lining of the shell that is mother of pearl.

The state of the art at the time of filing was that transgenic mollusks were produced using either autologous or heterologous promoters to drive expression of a foreign gene. However, the level of activity from various promoters and the length of time the transgene remained active was not predictable (Powers, 1997, USPN 5,675,061, column 15, lines 60-64). Powers disclosed that vertebrate retroviral promoters including CMV and RSV were not active in transgenic abalone generated by electroporation of DNA into fertilized eggs (column 15, lines 65-67). Powers further demonstrated that the activity of a transgene comprising the Drosophila β -actin promoter upstream of β-galactosidase was low in abalone compared to activity in Drosophila cells (column 8, lines 44-47) and, furthermore, was silenced over time (column 15, lines 60-64). However, Raynter (1996, WO 96/15662) used the RSV promoter to effectively drive expression of insulin in transgenic oysters, which promoted growth and resulted in increased size of the transgenic oysters (page 21, lines 15-20). Burns (USPN 5,969,211) also disclosed expression of β -galactosidase mediated by the RSV LTR (column 8, lines 27-30) in transgenic dwarf surfclams produced by retroviral infection. Cadoret (Journal of Biotechnology, 1997, Vol. 56, pp. 183-189) disclosed

expression of a luciferase reporter in transgenic oysters using both the CMV promoter and the Drosophila hsp70 promoter when transgenics were produced using high velocity particle bombardment. Cadoret demonstrated that the Drosophila hsp70 promoter had a greater efficiency of expression than the CMV promoter. The state of the art at the time of filing was that the level of efficiency and duration of expression of transgenes in transgenic mollusks was unpredictable and varied according to the promoter a species used.

1) The specification does not enable making a transgenic mollusk that secretes a colored protein into the pearl. The specification teaches using an adenoviral vector comprising the GFP gene (page 10, lines 14-17 and page 7, lines 1-12) under the control of the CAG promoter (Niwa, 1991, Gene, Vol. 108, pages 193-200; Kanegae, 1995, Nucl. Acids Res., Vol. 23, pages 3816-3821; Miyake, 1996, PNAS, Vol. 93, pages 1320-1324; http://bio.takara.co.jp/BIO_EN/Catalog_d.asp?C_ID=C0982) to make transgenic Pinctada fucata martensii (page 10, lines 17-23) with fluorescent tissues including fluorescent mantle tissue (page 11, Table 3). However, the specification does not teach that GFP is secreted from the mantle, which is necessary to obtain a colored pearl. Other teachings in the specification use a GFP fusion transgene where GFP is operably linked to either the prism protein promoter (page 11, lines 8-23) or mantle protein promoter (page 12, lines 15-27). The specification fails to provide enough information to determine the structure of the fusion genes. It is not clear where the linker was ligated, what coding sequences or secretion signals from the prism or mantle proteins were included, or how the fragments were "hybridized to obtain a fusion gene".

These teachings are not adequate to obtain GFP expression in the mantle and secretion into a pearl using a GFP transgene fusion. Therefore, the specification does not provide adequate guidance for one of skill in the art at the time the invention was made to overcome the unpredictability in the art described above to obtain the phenotype of interest, i.e. to obtain secretion of a color producing gene product into the pearl of a transgenic mollusk.

2) The transgenic mollusks claimed are used for generating a colored pearl (page 2, lines 20-22; page 14, lines 14-15). However, not all shellfish or mollusks, such as shrimp, snails, lobsters, octopus et al., generate pearls. Therefore, claims 1-8 should be limited to transgenic, pearl-producing mollusks such as Bivalvia or abalone.

3) Claims 1-8 are not enabled because they do not have a phenotype. The specification does not provide an enabled use for any transgenic mollusk without a phenotype that is different than wildtype, and that is caused by the transgene. Claims 4 and 5 are not enabled because they do not state the color is caused by the transgene or that it is obtained in the pearl. The specification does not provide an enabled use for a transgenic with a wild type phenotype.

4) The specification fails to provide an enabled use for a transgenic mollusk that merely expresses a foreign gene relating to coloring in any tissue. The purpose of the transgenic mollusk is to obtain expression of a color producing protein in the mantle and secretion into the pearl (page 2, lines 20-22; page 12, lines 10-12). The specification does not provide an enabled use for a transgenic mollusk that merely expresses a colorant in any tissue as claimed. It would require one of skill at the time the invention

was made undue experimentation to determine how to use a transgenic shellfish expressing a colorant gene in any tissue other than the pearl. Therefore, the claims should be limited to transgenic mollusks expressing a coloring gene in the mantle.

5) The specification fails to enable using any "gene relating to coloring" other than GFP (claims 4 and 5). As defined in the specification, a coloring gene includes substances that participate in pigment-formation reactions (page 3, lines 4-10). β-galactosidase, by itself, is not a colorant but is an enzyme capable of turning various substrates into various colored deposits. The specification does not teach the expression of a pigment-forming enzyme in the mantle. More specifically, the specification does not teach if pigment-producing reactions can be carried out in a pearl containing a coloring enzyme or how to carry out such reactions as to form a pigmented reaction product in the pearl. Is it necessary to supply the substrates as the pearl is being produced or can the substrates be provided and diffuse through the pearl after it is harvested? It would require one of skill in the art at the time the invention was made, undue experimentation to determine how to carry out a colorant-forming reaction in a pearl.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of parenthetical language renders claim 1 indefinite because it cannot be determined if the phrase "excluding a gene giving resistance to a virus" is to be included in the claim or not.

Claims 1-8 are indefinite because the metes and bounds of what applicants consider "desired" cannot be determined.

The term "shellfish" (claim 2) is indefinite. Not all shellfish, i.e. lobsters, crabs et al, are mollusks. Claim 2 depends from claim 1, which claims a transgenic mollusk. Thus, claim 2 fails to further limit claim 1 and is indefinite as it cannot be determined what is encompassed by the term "shellfish".

The term "pearl shell" (claim 3) is unclear. Term pearl shell is not defined in the specification and it is unclear how a mollusk is a "pearl shell".

The phrase "gene relating to coloring" (claims 4 and 5) is unclear. The specification defines "genes relating to coloring" as genes encoding pigments and genes encoding substances which participate in pigment formation-reactions in the body. β-galactosidase does not produce a pigment but can cause a pigment to be produced given exogenous substrates. GFP is not a protein with a color but is a fluorescent protein that emits wavelengths outside the visible color range. Thus, the metes and bounds of what applicants consider genes relating to color cannot be determined.

Claim 4 is indefinite because it does not clearly set forth that the colored tissue is a result of the gene relating to coloring.

Claim 5 is indefinite because it does not clearly set forth that the fluorescence is a result of expression of GFP.

The phrase "mollusk into which a desired foreign gene is introduced" (claim 1) is not a clear, positive limitation setting forth the structure of the mollusk. The phrase "mollusk comprising a desired foreign gene" would overcome this rejection.

The phrase "and which expresses said foreign gene" (claim 1) is not a clear, positive limitation setting forth the structure of the mollusk. The phrase "which expresses" reads as "is capable of expressing", which is not a clear positive step because it may not occur. Thus, the claim does not set forth that the protein is expressed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 1-4 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Burns (USPN 5,969,211).

Burns taught transgenic surf clams comprising DNA encoding β -galactosidase operably linked to an RSV promoter (col. 6, lines 8-9). The DNA was electroporated into fertilized eggs (col. 6, lines 21-24), the eggs developed into individuals and individuals that express β -galactosidase were generated(column 8, lines 28-30).

2) Claims 1-3, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Raynter (PCT/US95/14685).

Raynter taught generating transgenic oysters comprising DNA encoding human insulin functionally linked to the RSV LTR (pg. 21, lines 26-35). The DNA was electroporated into fertilized eggs (pg. 21, lines 1-2) and the eggs developed into individuals (pg. 21, lines 4-5) that expressed the transgene (pg. 21, lines 9-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 1-5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns (USPN 5,969,211) in view of Godwin (*PNAS,* 1998, vol. 95, pp. 13042-13047)

Burns taught transgenic surf clams comprising DNA encoding β -galactosidase operably linked to an RSV promoter (col. 6, lines 8-9). The DNA was electroporated into fertilized eggs (col. 6, lines 21-24), the eggs developed into individuals and individuals that express β -galactosidase were generated (column 8, lines 28-30). Burns did not teach the DNA encoded GFP.

However, Godwin taught the use of a GFP reporter gene in place of the β -galactosidase gene in transgenics (Abstract and page 13042, col. 2, "Vector Construction").

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to generate the transgenic surf clams expressing a marker protein as taught by Burns using the GFP reporter gene as taught by Godwin. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the β -galactosidase reporter gene with GFP because GFP provides the additional utility of a vital marker in allowing immediate visualization of the reporter without requiring the sacrifice of valuable transgenic animals (refer to Godwin, pg. 13042, column 1, lines 6-10).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

2) Claims 1-5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raynter (PCT/US95/14685) in view of Godwin (*PNAS,* 1998, vol. 95, pp. 13042-13047) and Burns (USPN 5,969,211).

Raynter taught generating transgenic oysters expressing human insulin by introducing the human insulin gene functionally linked to the RSV LTR (pg. 21, lines 26-35) into fertilized eggs (pg. 21, lines 1-2), the eggs developed into individuals (pg. 21, lines 4-5) and selecting those that express the transgene (pg. 21, lines 9-10). Raynter did not teach the use of GFP as a transgene.

However, Godwin taught the use of a GFP reporter gene in place of the β -galactosidase gene in transgenics (Abstract and page 13042, col. 2, "Vector Construction").

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to generate the transgenic oysters as taught by Raynter using the GFP reporter taught by Godwin. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the human insulin gene with the GFP gene because GFP was known as an easily detectable marker of transgenesis (Godwin, page 13042, column 1, lines 6-10) that allowed for the analysis of transgenic methods in mollusks. Use of GFP as a reporter allows immediate visualization of the reporter without requiring the sacrifice of valuable transgenic animals. The ease of detecting where expression occurs provides motivation to use marker genes in oysters instead of insulin. For example, Burns taught detecting marker gene expression in transgenic shellfish (column 8, lines 27-30), which allows one to easily determine where expression of the transgene occurs.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

3) Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns (USPN 5,969,211) in view of Ogawa (1995, Journal of Reproduction and Development, Vol. 41, pp. 379-382).

Burns taught transgenic surf clams comprising DNA encoding β -galactosidase operably linked to an RSV promoter (col. 6, lines 8-9). The DNA was electroporated into

fertilized eggs (col. 6, lines 21-24), the eggs developed into individuals and individuals that express β -galactosidase were generated (column 8, lines 28-30). Burns did not teach the injection of DNA into the testis.

However, Ogawa taught injection of a β -galactosidase reporter gene into mouse testis to generate transgenic mice (page 380, column 2, Results and Discussion 1st paragraph).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to generate the transgenic mollusks expressing a marker protein as taught by Burns by injecting the DNA into the testis as taught by Sato. One of ordinary skill in the art at the time the invention was made would have been motivated to generate transgenic mollusks using testicular injection because making a transgenic by injecting the testes is easier than injecting or electroporating numerous batches of eggs (Ogawa, page 381). Injecting the testes of a small number of males can provide a transgene source of sperm to fertilize countless numbers of eggs at any desired time, requiring only the mere task of mating.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner

MICHAEL C. WILSON
PATENT EXAMINER